FORM PTO-1390 (Modified) (REV 11-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: **199509US0PCT**

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR): **09/744247**

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/05137	**19 July 1999**	**30 July 1998**

TITLE OF INVENTION

NEW INJECTABLE FORMULATIONS CONTAINING RAMOPLANIN

APPLICANT(S) FOR DO/EO/US

Francesco PARENTI, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ Certificate of Mailing by Express Mail
20. ☒ Other items or information:

Request for Consideration of Documents Cited in International Search Report
Notice of Priority
Letter Regarding Small Entity Status
PCT/IB/304
PCT/IB/308

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/744247	PCT/EP99/05137	199509US0PCT

21. The following fees are submitted:	CALCULATIONS PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :	
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO $1,000.00	
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but Internation Search Report prepared by the EPO or JPO $860.00	
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO $710.00	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) $690.00	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) $100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$860.00
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	$0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	35 - 20 =	15	x $18.00	$270.00
Independent claims	1 - 3 =	0	x $80.00	$0.00
Multiple Dependent Claims **(check if applicable)**.			☐	$0.00
	TOTAL OF ABOVE CALCULATIONS		=	$1,130.00
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable)**.			☒	$565.00
	SUBTOTAL		=	$565.00
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).			+	$0.00
	TOTAL NATIONAL FEE		=	$565.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).**			☐	$0.00
	TOTAL FEES ENCLOSED		=	$565.00
			Amount to be: refunded	$
			charged	$

☒ A check in the amount of **$565.00** to cover the above fees is enclosed.

☐ Please charge my Deposit Account No. in the amount of to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **15-0030** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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Surinder Sachar
SIGNATURE

Norman F. Oblon
NAME

24,618
REGISTRATION NUMBER

1-30-01
DATE

199509US0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :

FRANCESCO PARENTI ET AL : ATTN: APPLICATION DIVISION

SERIAL NO: NEW APPLICATION :
(Based on PCT/EP99/05137)

FILED: HEREWITH :

FOR: NEW INJECTABLE FORMULATIONS:
CONTAINING RAMOPLANIN

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Prior to examination on the merits, please amend the above-identified application as follows.

IN THE CLAIMS

Please amend the claims as follows:

--3. (Amended) A formulation according to claim 2 wherein the fat emulsion product comprises as an oil phase vegetal oils [such as soybean, cottonseed oil, safflower oil or a mixture thereof], an emulsifier based on phospholipids, [preferably from egg source such as egg lecithin, soybean lecithin or a mixture thereof], and an additive as osmotic agent [such as sorbitol, glycerol, xylilol or a mixture thereof].

4. (Amended) A formulation according to claim 3 wherein the oil phase is in a range from 0.2 to 40 percent (weight/vol)[, preferably, from 4 to 25 percent, more preferably, from 8 to 18 percent and, most preferably, from 8 to 10 percent] of the final formulation.

5. (Amended) A formulation according to [any of claims 1 to 4] claim 1 wherein the fat emulsion product employed for the preparation of said formulation contains from 2 to 40 percent, (weight/vol),[preferably, from 5 to 25 percent, more preferably from 7 to 20 percent] of oil phase, from 0.2 to 5 percent, (weight/vol), [preferably, from 0.6 to 2 percent, more preferably, from 0.5 to 1.5 percent] of emulsifier and an additive in an amount suitable to control osmolarity[, preferably in a range from 1.5 to 5 percent (weight/vol), preferably from 2 to 3 percent].

6. (Amended) A formulation according to [any of claims 1 to 5] claim 1 wherein the oil phase contains long chain fatty acids in the form of triglycerides in the following proportions by weight:

linoleic acid	40-70%
oleic acid	15-30%
palmitic acid	5-15%
linoleic acid	3-12%
stearic acid	2-6%

7. (Amended) A formulation according to [any claims 1 to 6] claim 1 wherein the fat emulsion product employed for the preparation of said formulation comprises a composition selected from those reported in the following tables:

	Fat emulsion product 1	Fat emulsion product 2	Fat emulsion product 3
Soybean oil (w/vol)	10%	20%	5%

Safflower oil (w/vol)	--	--	5%
Egg yolk phospholipids (w/vol)	1.2%	1.2%	1.2%
Glycerol (w/vol)	2.25%	2.25%	2.5%
Fatty acids composition of vegetable oils (w/vol)			
Linoleic acid	50%	50%	65.8%
Oleic acid	26%	26%	17.7%
Palmitic acid	10%	10%	8.8%
Linolenic acid	9%	9%	4.2%
Stearic acid	3.5%	3.5%	3.4%
Osmolarity (mOsm/L)	260	268	276
Approximate pH	8	8	8
Fat particle size (μm)	0.5	0.5	0.4
Caloric value (cal/ml)	1.1	2.0	1.1
Size (ml)	50, 100	50, 100	25, 50
	250 or	250 or	100, 200
	500	500	Or 500
	Fat emulsion product 4	Fat emulsion product 5	Fat emulsion product 6
Soybean oil (w/vol)	10%	10%	20%
Safflower oil (w/vol)	10%	--	--
Egg yolk phospholipids (w/vol)	1.2%	1.2%	1.2%
Glycerol (w/vol)	2.5%	2.5%	2.5%
Fatty acids composition of vegetable oil (w/vol)			
Linoleic acid	65.8%	54.5%	54.5%
Oleic acid	17.7%	22.4%	22.4%
Palmitic acid	8.8%	10.5%	10.5%
Linolenic acid	4.2%	8.3%	8.3%
Stearic acid	3.4%	4.2%	4.2%

Osmolarity (mOsm/L)	258	284	292
Approximate pH	8.3	8.3	8.3
Fat particle size (μm)	0.4	0.4	0.4
Caloric value (cal/ml)	2.0	1.1	2.0
Size (ml)	25, 50	100, 200	200 or
	200 or	Or 500	550
	500		

and water for injection q.s. to 100%.

8. (Amended) A formulation according of claims 6 [or 7] wherein soybean oil and/or cottonseed oil and/or safflower oil are totally or partially replaced by a mixture of long chain fatty acids in the form of triglycerides to form a composition wherein said fatty acids are present in the respective proportions indicated in said claims and, optionally part of the above oils or long chain fatty acids is substituted by medium chain (C_6-C_{12}) triglycerides.

9. (Amended) A formulation according to [any of claims 1 to 8] claim 1 wherein the concentration of the oil phase is between 4 and 25% (weight/vol)[, preferably, between 8 and 18%, more preferably between 8 and 10%] of the final formulation.

11. (Amended) A formulation according to [any one of claims 1 to 10] claim 1 wherein ramoplanin is present at a concentration between 1 and 20 mg/ml[, preferably from 1.5 to 15 mg/ml, most preferably, from about 3 to about 5 mg/ml].

12. (Amended) A formulation according to [any of claims 1 to 11] claim 1 wherein the pH of the final formulation is lower than 8[, preferably, lower than 7].

13. (Amended) A formulation according to [any of claims 1 to 10] claim 1 wherein the pH of the final formulation is between 4 and 6.5.

14. (Amended) A formulation according to [any one of claims 1 to 13] claim 1 for treatment of infections caused by agents that are susceptible to ramoplanin or an antibiotic of the ramoplanin family.

15. (Amended) A formulation according to [any one of claims 1 to 13] claim 1 for the treatment of serious Gram positive infections - such as bacteremia, endocarditis or pneumonia.

16. (Amended) A formulation according to [any one of claims 1 to 13] claim 1 for the treatment of severe infections caused by Gram positive drug-resistant or multiresistant microorganisms such as coagulase positive and negative staphylococci, penicillin-resistant streptococci or glycopeptide resistant enterococci.

17. (Amended) A formulation according to [any one of claims 1 to 16] claim 1 wherein ramoplanin factor A_2 is present in an amount of at least 75%.

18. (Amended) A pharmaceutical composition which consists of a ready to use dosage form or of a kit comprising separate packagings or containers containing ramoplanin or a member of ramoplanin family and the fat emulsion product for constitution of a formulation according to[any of claims 1 to 17] claim 1.--

Please add the following claims:

--20. The formulation according to claim 3, wherein said vegetal oil are selected from the group consisting of soybean oil, cottonseed oil, safflower oil and mixtures thereof.

21. The formulation according to claim 3, wherein said phospholipids are from an egg source.

22. The formulation according to claim 21, wherein said phospholipids are selected from the group consisting of egg lecithin, soybean lecithin, and mixtures thereof.

23. The formulation according to claim 3, wherein said osmotic agent is selected from the group consisting of sorbitol, glycerol, xylilol and mixtures thereof.

24. The formulation according to claim 4, wherein the oil phase is in the range of from 4 to 25 percent of the final formulation.

25. The formulation according to claim 4, wherein the oil phase is in the range of from 8 to 18 percent of the final formulation.

26. The formulation according to claim 4, wherein the oil phase is in the range of from 8 to 10 percent of the final formulation.

27. The formulation according to claim 5, wherein the fat emulsion product contains from 5 to 25 percent of the oil phase.

28. The formulation according to claim 5, wherein the fat emulsion product contains from 7 to 20 percent of the oil phase.

29. The formulation according to claim 5, wherein the fat emulsion product contains from 0.6 to 2 percent of the emulsifier.

30. The formulation according to claim 5, wherein the additive is in an amount from 1.5 to 5 percent.

31. The formulation according to claim 5, wherein the additive is in an amount from 2 to 3 percent.

32. The formulation according to claim 9, wherein the concentration of the oil phase is from 8 to 18 percent of the final formulation.

33. The formulation according to claim 11, wherein the ramoplanin is present in a concentration of from 1.5 to 15 mg/ml.

34. The formulation according to claim 11, wherein the ramoplanin is present in a concentration of from 3 to 5 mg/ml.

35. The formulation according to claim 12, wherein the pH of the final formulation is lower than 7.--

SUPPORT FOR THE AMENDMENT

Support for Claims 20-23 is found in Claim 3. Support for Claims 24-26 is found in Claim 4. Support for Claims 27-31 is found in Claim 5. Support for Claim 32 is found in Claim 9. Support for Claims 33-34 is found in Claim 11. Support for Claim 35 is found in Claim 12.

REMARKS

Claims 1-35 are active in the present application. The claims are amended for clarity and to remove multiple dependencies. No new matter is added. An action on the merits and allowance of the claims is solicited.

Respectfully submitted,

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NEW INJECTABLE FORMULATIONS CONTAINING RAMOPLANIN

The present invention relates to a new injectable formulation of ramoplanin or a compound of the ramoplanin family. More particularly, the injectable formulations of the invention are particularly suitable for intravenous (i.v.) administration.

Ramoplanin (INN) is a known member of the cyclic peptide antibiotics more precisely known as glycolipodepsipeptides which has been described in US 4,303,646 and 4,328,316. Originally it has been named antibiotic A 16686. It is a complex substance whose separate factors A_1, A_2 and A_3 have been described in US 4,427,656.

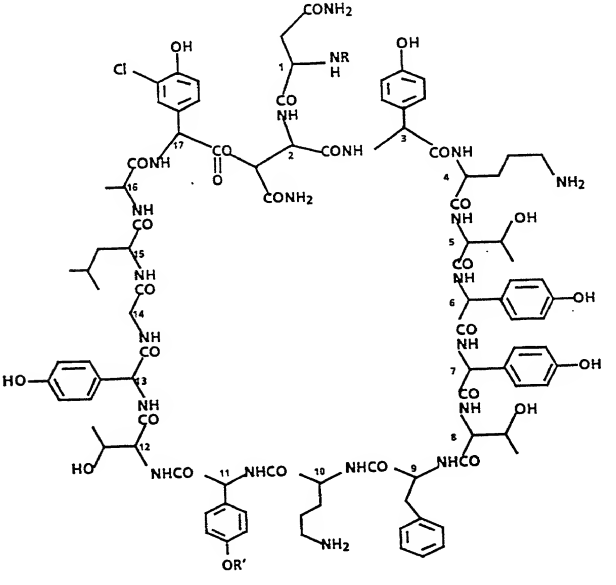
Ramoplanin factors A'_1, A'_2 and A'_3 have been described in EP-B-318680, the aglycones of any of the above factors have been described in US 5,491,128 while the tetra hydrogenated derivatives of any of the above factors have been described in US 5,108,988. A method for selectively increasing the ratio of single major components A_2 and A_3 is described in EP 0259780. All the above mentioned patents are incorporated herein by reference.

The structure of ramoplanin and its factors and derivatives have been described in several articles and publications, see R. Ciabatti et al., J. Antib. 1989, 254-267, J. K. Kettenring et al., J. Antiob. 1989, 268-275, R. Ciabatti and B. Cavalleri, Bioactive Metabolites from Microorganisms, Elsevier Science

Publisher, 1989, 205-219 and M. Kurz and W. Guba, Biochemistry 1996, 35, 12570-12575.

N.J. Skelton et al. in J. Am. Chem. Soc. 1991, 113, 7522-7530 describe another member of this family, which they call Ramoplanose.

These compounds can be represented by the following formula (Formula I):



FORMULA I

wherein:

R represents $-CO-CH=CH-CH=CH-CH_2-CH_2-CH_3$,
$-CO-CH=CH-CH=CH-CH_2-CH(CH_3)_2$,
$-CO-CH=CH-CH=CH-CH_2-CH_2-CH(CH_3)_2$,
$-CO-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_3$,
$-CO-CH_2-CH_2-CH_2-CH_2-CH_2-CH(CH_3)_2$ or
$-CO-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH(CH_3)_2$

R' represents alpha-D-mannopyranosyl or 2-O-alpha-D-mannopyranosyl-alpha-D-mannopyranosil,

or

R' represents 2,3-O-di[alpha-D-mannopyranosyl]-D-mannopyranosyl when R represents $-CO-CH=CH-CH=CH-CH_2-CH(CH_3)_2$,

a pharmaceutically acceptable acid addition salt thereof, or a mixture thereof in any proportion.

The configuration of the double bonds of the unsaturated moieties reported above in the definition of R have been found to be 2(E) or *cis* and 4(Z) or *trans* in the literature reported above.

The following table specifies the meanings for R and R' of the single factors or derivatives with reference to the above formula:

Factor	R	R'
A_1	-CO-CH=CH-CH=CH-CH_2-CH_2-CH_3	2-O-alpha-D-manno-pyranosyl-alpha-D-mannopyranosyl
A_2	-CO-CH=CH-CH=CH-CH_2-$CH(CH_3)_2$	2-O-alpha-D-manno-pyranosyl-alpha-D-mannopyranosyl
A_3	-CO-CH=CH-CH=CH-CH_2-CH_2-$CH(CH_3)_2$	2-O-alpha-D-manno-pyranosyl-alpha-D-mannopyranosyl
A'_1	-CO-CH=CH-CH=CH-CH_2-CH_2-CH_3	Alpha-D-mannopyranosyl
A'_2	-CO-CH=CH-CH=CH-CH_2-$CH(CH_3)_2$	Alpha-D-mannopyranosyl
A'_3	-CO-CH=CH-CH=CH-CH_2-CH_2-$CH(CH_3)_2$	Alpha-D-mannopyranosyl

The aglycones correspond to the compounds reported above wherein R' represents hydrogen while the tetrahydrogenate derivatives correspond to the compounds reported above wherein the mojety R is fully hydrogenated.

Ramoplanose is reported to correspond to "factor A_2" wherein R' represents 2,3-O-di[alpha-D-mannopyranosyl]-D-mannopyranosyl.

In the following description and claims, the term "ramoplanin" refer to a ramoplanin complex wherein factor A_2 is the major component, with a small amounts of factors A'_2, A_1, A'_1, A_3, A'_3 and other related substances accounting for the remainder of this active ingredient.

Particularly preferred is "ramoplanin" wherein factor A_2 represents at least 75% of the active ingredient.

"A member of the ramoplanin family" refers to any of the compounds reported above that are represented by Formula I, any salt or any mixture thereof in any proportion.

Ramoplanin as well as any members of the ramoplanin family are unsuitable for i.v. administration because of drawbacks such as swelling and progressive necrotization at the site of injection, and haemolysis as revealed by urine discoloration.

The formulations of the invention contain ramoplanin or a member of the ramoplanin family in admixture with a fat emulsion product for intravenous administration.

In general, for i.v. administration purposes according to this invention, it is suitable to utilize liquid compositions wherein ramoplanin or a member of ramoplanin family is present in concentration from 1 to 20 mg/ml, preferably, from 1.5 to 15 mg/ml, most preferably, from about 3 to about 5 mg/ml.

In the current description and claims the expressions "fat emulsion product for intravenous injection" or "fat emulsion product" identify any of those fat emulsion products suitable for intravenous administration via a peripheral vein or by a central venous infusion that are currently used mainly to assure calories intake when parenteral nutrition is required. Examples of these substances are for instance reported in US Pharmacopeia, Martindale, The Extra Pharmacopeia (31st edition, 1996, page 1377) or VIDAL

1996, page 814. The above expressions include also those emulsions used as colloidal drug carriers, examples of which are reported in the book "Submicron Emulsions in Drug Targeting and Delivery" edited by S. Benita, Horwood Academic Publishers, 1998, at pages 119-122. All above cited publications are incorpored hereby by reference.

The above said fat emulsion products are largely based on an oil phase stabilized by emulsifiers, like phospholipids, poloxamers or other polyoxyethylene derivatives such as, for instance, polysorbates or polyoxyethylene castor oil.

Typically, a fat emulsion product suitable for preparing a formulation of the invention comprises an oil phase (usually 2-40%, preferably, 5-25% weight/vol), preferably consisting of vegetable oils such as soybean oil, safflower oil and cottonseed oil, emulsifiers (usually 0.2-5%, preferably, 0.5-2% weight/vol), preferably based on phospholipids of egg source such as, egg lecithin or soybean lecithin, and additives as osmotic agents such as glycerol, sorbitol and xylitol.

These fat emulsion products, as commercially available, are emulsions comprising the above mentioned oil phase, emulsifiers and additives dispersed in water for injection and the oil phase is generally present in the emulsion in a percentage (weight/vol) of 5 to 25%. For preparing the i.v. administrable formulation of this invention, the fat emulsions product may be used as such or diluted with saline or water for injection added with an osmotic agent (e.g. glucose) to decrease

the oil phase concentration to a lower value and, at the same time, maintaining the desired osmolarity.

In general, if the concentration of ramoplanin or a member of ramoplanin family in the formulation is low, it is possible to lower the percentage of the oil phase in said i.v. formulation.

For instance, with ramoplanin concentrations of about 10 mg/ml, the percentage of the oil phase in the i.v. formulations of the invention may range between 4 and 40% (weight/vol) although are preferred those i.v. fat emulsions wherein the oil phase is between 4 and 25%, and, more preferably, between 8 and 18%, with the range 8-10%being currently the most preferred concentration.

With ramoplanin concentrations of about 1 mg/ml the percentage of the oil phase in the i.v. formulation can be lowered to a range between 0.2 and 10% (weight/vol).

Generally, the osmolarity of the final i.v. formulation is between 250 and 300 mOsm/L, while the value of the pH must be compatible with the stability of ramoplanin (or a member of the ramoplanin family), and, therefore, usually, it should not be higher than 8.

As known in the art, particle size of the emulsion needs to be controlled for a proper i.v. administration, and this is accomplished through the conventional preparation and final formulation procedures.

Examples of fat emulsion products that can be conveniently used according to the present invention are those listed at page 120 of the above cited book: "Submicron Emulsion in Drug Targeting and Delivery" where the oil phase consists of soybean oil, cottonseed oil, safflower oil or mixture thereof.

Soybean oil, cottonseed oil and safflower oil contain long chain fatty acids comprising mainly linoleic acid, oleic acid, palmitic acid, linolenic acid and stearic acid, essentially in the form of triglycerides.

Soybean oil, cottonseed oil and safflower oil can be totally or in part substituted by any mixtures of the above fatty acids in the form of triglycerides having a percent (weight/weight) composition substantially similar to that of the above oils or their mixtures. Moreover, part of the above mentioned vegetable oils or long chain fatty acids triglycerides may be substituted by medium chain (C_6-C_{12}) triglycerides.

Typically, the fat emulsion product used for the preparation of the i.v. formulations of this invention contains an oil phase in a range from 2 to 40 percent (weight/vol), preferably, from 5 to 25 percent, more preferably from 7 to 20 percent, emulsifier(s) in a range from 0.2 to 5 percent (weight/vol), preferably, from 0.6 to 2 percent more preferably from 0.5 to 1.5 percent, and the additive is in an amount suitable to control osmolarity, preferably, in a range from 1.5 to 5 percent (weight/vol), more preferably preferably from 2 to 3 percent.

In said oil phase consisting of soybean oil, cottonseed oil or safflower oil or mixture thereof, or in the fatty acids mixtures which may substitute totally or in part the above oils, the fatty acids triglycerides are usually present in the following percent (weight/weight) proportion indicated between brackets: linoleic acid (40-70%), oleic acid (15-30%), palmitic acid (5-15%), linolenic acid (3-12%), stearic acid (2-6%).

As indicated above, for the preparation of the i.v. formulations of this invention, the above said fat emulsion products are used as such or are diluted in a isoosmotic water solution for injection to a concentration of the oil phase in the final composition that is at least 0.2% (weight/vol), normally, depending on the concentration of ramoplain or a member of ramoplanin family which is present in the final composition.

According to a preferred embodiment of this invention, those fat emulsion products that are currently available under the trade names Intralipid®, Liposyn® and Lipofundin® may be utilized. For instance, Intralipid® (Kabi Vitrum/Pharmacia) and Liposyn® II and Liposyn® III (Abbott), have composition and physico-chemical properties as reported below:

Table I. Composition and characteristics of Various Intravenous Fat Emulsions

Components or Characteristics	Intralipid® (Kabi-Vitrum/Pharmacia)		Liposyn® II (Abbott)		Liposyn® III (Abbott)	
Soybean oil (w/vol)	10%	20%	5%	10%	10%	20%
Safflower oil (w/vol)	--	--	5%	10%	--	--
Egg yolk phospholipids (w/vol)	1.2%	1.2%	1.2%	1.2%	1.2%	1.2%
Glycerol (w/vol)	2.25%	2.25%	2.5%	2.5%	2.5%	2.5%
Water for injection	QS	QS	QS	QS	QS	QS
Fatty acids composition of vegetable oils (w/w)						
Linoleic acid	50%		65.8%		54.5 %	
Oleic acid	26%		17.7%		22.4 %	
Palmitic acid	10%		8.8%		10.5 %	
Linolenic acid	9%		4.2%		8.3%	
Stearic acid	3.5%		3.4%		4.2%	
Osmolarity (mOsm/L)	260	268	276	258	284	292
Approximate pH	8	8	8	8.3	8.3	8.3
Fat particle size (µm)	0.5	0.5	0.4	0.4	0.4	0.4
Caloric value (cal/ml)	1.1	2.0	1.1	2.0	1.1	2.0
Size (ml)	50, 100	50, 100	25, 50	25, 50	100,200	200,500
	250,500	250,500	100,200	200,500	500	
			500			

As stated above, in the formulations according to this invention ramoplanin or a member of the ramoplanin family as defined above is generally present in the compositions of the invention in an amount of 1 to 20 mg/ml, with a range of 1.5 to 15 mg/ml being currently preferred, and a range from about 3 to about 5 mg/ml being the most preferred one.

Typically, the composition of the invention is a composition wherein the oil phase in the final fat emulsion is between 0.2 and 40%(weight/vol), with a range 4-25% being preferred, a range 8-18% being more preferred and with the range 8-10% being currently most preferred. However, as mentioned above, the proportion of the oil phase may be adjusted to the one of the antibiotic and to lower amounts of ramoplanin may correspond lower amounts of oil phase in the composition

Experiments with representative examples of the compositions of the invention have shown a good tolerability at the site of injection, in particular in comparison with the effects of conventional i.v. preparations of the same active principle.

The results of a first set of tolerability studies in representative examples of formulations of the invention in rats at a concentration of ramoplanin of 10 mg/ml (dose 20 mg/kg, administration volume 2 ml/kg), in comparison with a conventional i.v. formulation of the same active principle, are summarized in the following.

More particularly, ramoplanin in a conventional acqueous vehicle (0.9% saline) or in the formulations of the invention wherein the proportion of the oil phase in the total formulation is between 2 and 8% (weight/vol) is administered to rats (3-5 animal/group) at a dose of 20 mg/kg (drug concentration 10 mg/ml). The administered volume is 2 ml/kg, according to the animal weight on the day of administration, and the injection speed is 0.1 ml/sec. The intravenous administration is into the caudal vein. Treatments are planned for three days at 24 hours intervals. Control rats receive either 0,9% saline or an equivalent volume of Intralipid® 10%. Behavior and physical appearance are observed frequently the day of dosing. Urine appearance is also recorded within 3 h after each daily treatment. Rats are sacrified 24 h after the last treatment. The results of these experiments are summarized in Table II.

Table II. Urine appearance, gross pathology at the injection site and clinical observations of rats treated with ramoplanin formulated with Intralipid® or in a conventional acqueous vehicle (0.9% saline)

Groups	No. Animals	Saline (w/vol)	Intralipid® (a) (w/vol)	Ramoplanin concentration	Urine Appearance (b)	Gross Pathology at the injection site (c)
A	3	0.9%	--	--	Normal	Normal
B	4	0.9%	--	10 mg/ml (d)	Red-brown	Dark, discolored tails
C	3	--	10%		Normal	Normal
D	5	--	8%	10 mg/ml	Normal	Normal
E	5	--	4%	10 mg/ml	Normal	Normal
F	5	--	2%	10 mg/ml	Red-brown	Dark, discolored tails

(a) In water for injection, q.s. 100%

(b) Visual examination performed within 2-3 h after each scheduled treatment

(c) Examinations performed at the end of the three scheduled treatments

(d) Corresponding to a dose of 20 mg/kg

Treatments with ramoplanin at a concentration of 10 mg/ml in conventional aqueous vehicle or in formulation with 2% (weight/vol) of oil phase caused darkness or discoloration at the injection site (tail). In contrast, treatment with the formulations of the invention wherein the oil phase was 4% (weight/vol) or higher was well tolerated. Tails did not show any sign of necrotic inflammation.

After the immediate postdose period of each treatment (3 h) with the formulations of the invention wherein the oil phase was 4% (weight/vol) or higher, the urine appeared light straw to dark yellow in colour. In contrast, rats given a 2% (weight/vol) oil phase formulation or ramoplanin in conventional aqueous vehicle developed red to red-brown urine, within the same postdose period.

A second set of experiments was carried out to determine tolerability of the formulation of the invention according to the same procedure described above but administering a dose corresponding to 10 mg/kg instead of 20 mg/kg to several groups of three rats for 3 days at 24 hours intervals with. The concentration of ramoplanin in the formulation was 1 mg/ml instead of 10 mg/ml and the volume of the formulation administered to each rat was 10 ml/kg instead of 2 ml/kg. The Intralipid® fat emulsion product was added in several different proportion as represented in the following Table III where the same parameters considered in Table II are reported. The rats were killed 24 h after the last treatment.

Table III. Urine appearance, gross pathology at the injection site and clinical observations of rats treated with ramoplanin formulated with Intralipid® or in a conventional acqueous vehicle (0.9% saline)

Groups	No. Animals	Saline (w/vol)	Intralipid® (w/vol) (a)	Ramoplanin concentration	Urine Appearance (b)	Gross Pathology at the injection site (c)
A	3	0.9%	--	1 mg/ml (d)	Red-brown	Dark tails (2/3)
B	3		9%	1 mg/ml	Normal	Normal
C	3	--	1%		Normal	Normal
D	3	--	0.5%	1 mg/ml	Normal	Normal
E	3	--	0.2%	1 mg/ml	Normal	Normal
F	3	--	0.1%	1 mg/ml	Red-brown	Discolored tails (3/3)

(a) In water for injection, q.s. 100%

(b) Visual examination performed within 3 h after each scheduled treatment

(c) Examinations performed at the end of the three scheduled treatments

(d) Corresponding to a dose of 10 mg/kg

The above data show that ramoplanin at a concentration of 1 mg/ml can be safely administered intravenously to experimental animals at a dosage of 10 mg/kg when the drug is appropriately formulated according to this invention in emulsion compositions containing Intralipid® in such amount that the oil phase is at least 0.2 per cent (w/vol) of the total formulation.

The effectiveness of representative examples of the compositions of the invention in experimental animal models can be demonstrated in several acute septicemia experiments in immunocompetent or neutropenic mice and in experiments of endocarditis and pneumococcal lobar pneumonia in rats.

Experimental septicemia is induced by inoculating intraperitoneally (5-6 animal/dose/treatment group) a bacterial suspension of either a clinical isolate of a methicillin resistant staphylococcus (*Staph. aureus* L613) or streptococcus strain (*Strep. pneumonia* L 44) in immunocompetent mice or a clinically isolated glycopeptide resistant enterococcus strain (*Ent. faecium* L569) in neutropenic mice. Immunocompetent mice are male and female CD_1 mice (Charles River Labs., Calco, Italy) weighting 18-22 g while neutropenic mice are 6-8 weeks old female NMRI mice (Iffa Credo, France).

Untreated animals die within 24-72 h after infection. Antibiotic treatment begins within 10 min after injection. Ramoplanin at various concentration is administered intravenously in conventional aqueous

vehicle or in the formulation of the invention in 8% (weight/vol) oil phase fat emulsion. Gentamicin, vancomycin, teicoplanin and rifampicin can be included as comparator drugs. The 50% effective dose (ED_{50}) and 95% confidence limits are calculated by the Spearman-Karber method from the percentage of animal surviving at day 10.

The animals are treated twice, first 10 min from infection and then 24 h later.

When the gentamicin or vancomycin are employed as comparators, they are administered subcutaneously and the second shot is given 5 h after infection. Rifampicin and teicoplanin are administered subcutaneously in single dose 10 min after infection.

Results of experiments conducted as described above are reported in the following table:

Table IV. ED_{50} of ramoplanin in experimental septicemia in mice.

Strain (animal)	**Formulation**	**ED_{50} mg/kg/dose (95% confidence limits)**
VanA *Ent.faecium* L 569 (neutropenic mice)[a]	Ramoplanin in 0.9% saline	**5.1 (d)**
	Ramoplanin in 8% Intralipid®	**1.7 (1.4-2.0)**
Staph. aureus L 613 (immunocompetent mice)[b]	Ramoplanin in 0.9% saline	**4.3 (3.1-6.0)**
	Ramoplanin in 8% intralipid®	**5.1 (3.9-6.5)**
Strep. pneumonia L 44 (immunocompetent mice)[c]	Ramoplanin in 0.9% saline	**0.06 (d)**
	Ramoplanin in 8% Intralipid®	**0.06 (d)**

[a] ED_{50} of comparators were as follows: gentamicin 50.6 (37.3-68.7), rifampicin 1.2 (0.9-1.5), vancomycin > 90%.

[b] ED_{50} of comparator (teicoplanin) was 5.4 (4.3-6.9).

[c] ED_{50} of comparator (teicoplanin) was 0.79 (0.65-0.96).

[d] Confidence limit could not be calculated because survival was either 0 or 100% in each treatment group.

Endocarditis experiments can be performed in experiment animals (rats) with isolates of staphylococci or enterococci. A polyethylene catheter is inserted through the aortic valve into the left ventricle of the animal via the right carotid artery. Two days later, the animals are infected i.v. Treatment begins the day after infection and continues for a total of 5 days. Surviving animals are killed on day 7 after infection. The hearts of all animals are homogenized and processed to determine bacterial load, that is expected to be substantially reduced in the treatment group receiving the formulations of the invention, in comparison with untreated controls.

Pneumonia experiments can be performed in both immunocompetent and neutropenic rats with e.g. a clinically isolated penicillin-resistant *Strep. pneumoniae* strain. Anesthetized animals are infected by surgical intrabronchial instillation via intratracheal intubation, with a 40 µl inoculum containing approximately 10^6 to 10^7 $\log_{10}$ CFU (colony forming units) of *Strep.pneumoniae* and are allowed to recover. Therapy is initiated 12 h after infection and continued for a total of three days. Surviving animals are killed on day 4 after infection. The lungs of all animals are homogenized and processed to determine bacterial load, that is expected to be substantially reduced in the treatment group receiving the formulations of the invention, in comparison with the untreated control.

The results reported above show that the formulations of the invention are in general well

tolerated, in particular at the injection site, as demonstrated by the absence of necrotic inflammation and urine discoloration.

The results indicate that the delivered drug is effective in treating infections caused also by multiresistant microorganisms.

The formulations of the invention therefore can be effectively administered to a patient in need thereof to control or cure infections sustained by microorganisms that are known to be susceptible to ramoplanin or an antibiotic of the ramoplanin family.

Particularly preferred is the use of the formulations of the invention in antibiotic treatment of serious Gram positive infections such as bacteremia, endocarditis and pneumonia. In particular the use of the formulations of the invention is expecially suitable for systemic treatment of severe infections caused by Gram positive resistant or multiresistant microorganisms, such as coagulase-positive and negative staphylococci, penicillin resistant streptococci or glycopeptide resistant enterococci.

In the present disclosure, the term "patient" is intended to refer to warm blooded animals such as rodents, felines, equines, bovids, and primates, including humans. Preferred as "patients" according to the invention, in addition to humans, are pet and farm animals.

An example of dosage range of ramoplanin or a member of the ramoplanin family that can be administered through formulation of the invention, that is predicted to be effective for human therapy, is preferably between 0.5 and 1 g/die, while a preferred formulation contains about between 1 and 20 mg/ml, preferably, between 1.5 and 15 mg/ml, most preferably between about 3 to about 5 mg/ml of ramoplanin or a member of ramoplanin family.

Particularly preferred is the use of the formulations of the invention in severe enterococcal infections, particularly those attributable to vancomycin-resistant strains, for which no really effective treatment is currently available (see for instance M.B. Edmond et al., Clinical Infectious Diseases, 1996; 23: 1234-1239) as well as infections wherein penicillin-resistant streptococci are present.

In such treatments, the formulation of the invention is preferably employed as a slow infusion by a central vein.

The formulations of the invention are prepared according to the conventional techniques, on the basis of the present disclosure. The pH of the final preparation is lower than 7 and preferably between 4 and 6.5, with a pH between 5.5 and 6.5 being currently most preferred.

If necessary the pH of the final formulation is adjusted to the desired value by the known procedures.

The ramoplanin (or a member of ramoplanin family) i.v. formulation of this invention can be in the form of a ready to use dosage form containing both the antibiotic and the fat emulsion product or can be in the form of a kit comprising separate packagings or containers containing ramoplanin (or a member of ramoplanin family), and the fat emulsion product for constitution of said i.v. formulation when use is needed. In particular, said kit may consist of vials or similar containers containing the dose of lyophylized sterile antibiotic, ampuls containing water for injection in amount sufficient to dissolve the antibiotic and bottles containing the sterile fat emulsion product in amount appropriate for constituting the desired i.v. formulation.

Examples of specific formulations of the invention and formulation procedures are reported below.

Table V. Formulations of ramoplanin (10 mg/ml) in varying dilutions of Intralipid®.

	10% (w/vol) Intralipid (ml)	5% Glucose (w/vol)	50 mg/ml Ramoplanin (ml)	Intralipid® / Ramoplanin
A	8	--	2	8% (w/vol) / 10 mg/ml
B	4	4	2	4% (w/vol) / 10 mg/ml
C	2	6	2	2% (w/vol) / 10 mg/ml

Operatively, to 10% Intralipid® (Pharmacia), under moderate stirring, the glucose solution is slowly added followed by the ramoplanin solution.

The solution of ramoplanin in distilled water is prepared by dissolving 562 mg of ramoplanin (89% potency determined by a HPLC assay) in distilled water (5 ml) and then bringing to the final volume (10 ml).

Table VI. Formulations of ramoplanin (1 mg/ml) in varying dilutions of Intralipid®.

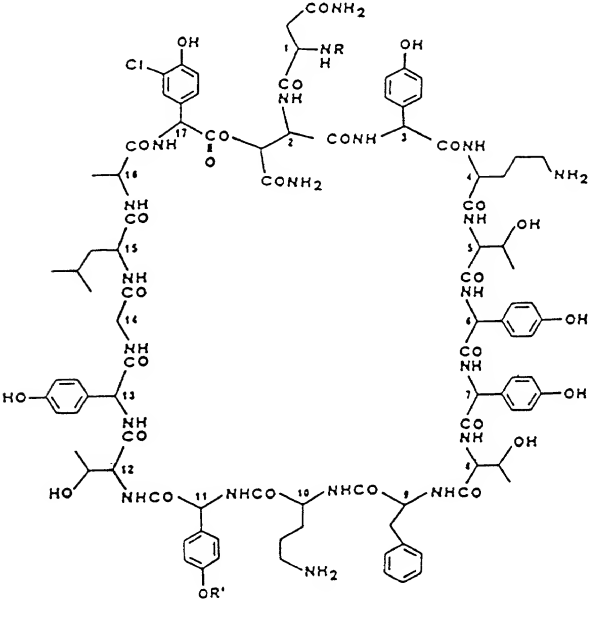
	10% (w/vol) Intralipid (ml)	0.9% Saline (w/vol)	10 mg/ml Ramoplanin (ml)	Intralipid® / Ramoplanin
D	9	--	1	9% / 1 mg/ml
E	1	8	1	1% / 1 mg/ml
F	0.5	8.5	1	0.5% / 1 mg/ml
G	0.2	8.8	1	0.2% / 1 mg/ml

A solution of ramoplanin 10 mg/ml of activity was prepared in NaCl 0.9% (w/vol). The solution was sterilized by filtration with 0.22 µm pore-size filters.

1 ml of the ramoplanin solution was added to an aliquot of Intralipid® diluted to the desired concentration by slow addition of the appropriate volume of 0.9% NaCl. The mixture was vigorously shaken to obtain a homogeneous dissolution in the fat emulsion.

CLAIMS

1. Pharmaceutical formulation for intravenous administration which comprises ramoplanin or a member of the ramoplanin family of formula I



FORMULA I

Wherein:

R represents $-CO-CH=CH-CH=CH-CH_2-CH_2-CH_3$,
$-CO-CH=CH-CH=CH-CH_2-CH(CH_3)_2$,
$-CO-CH=CH-CH=CH-CH_2-CH_2-CH(CH_3)_2$,
$-CO-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_3$,
$-CO-CH_2-CH_2-CH_2-CH_2-CH_2-CH(CH_3)_2$ or
$-CO-CH_2-CH_2-CH_2-CH_2-CH_2-CH2-CH(CH_3)_2$

R' represents alpha-D-mannopyranosyl or 2-O-alpha-D-mannopyranosyl-alpha-D-mannopyranosyl, or

R' represents 2,3-O-di[alpha-D-mannopyranosyl]-D-mannopyranosyl and R represents $-CO-CH=CH-CH=CH-CH_2-CH(CH_3)_2$,

a pharmaceutically acceptable acid addition salt thereof, or a mixture thereof in any proportion,

in admixture with an amount of fat emulsion product for intravenous administration wherein the concentration of the oil phase is at least 0.2% (weight/vol).

2. A formulation according to claim 1 wherein the fat emulsion product comprises an oil phase, an emulsifier and an additive as an osmotic agent.

3. A formulation according to claim 2 wherein the fat emulsion product comprises as an oil phase vegetal oils such as soybean, cottonseed oil, safflower oil or a mixture thereof, an emulsifier based on phospholipids, preferably from egg source such as egg lecithin, soybean lecithin or a mixture thereof, and an

additive as osmotic agent such as sorbitol, glycerol, xylilol or a mixture thereof.

4. A formulation according to claim 3 wherein the oil phase is in a range from 0.2 to 40 percent (weight/vol), preferably, from 4 to 25 percent, more preferably, from 8 to 18 percent and, most preferably, from 8 to 10 percent of the final formulation.

5. A formulation according to any of claims 1 to 4 wherein the fat emulsion product employed for the preparation of said formulation contains from 2 to 40 percent, (weight/vol), preferably, from 5 to 25 percent, more preferably from 7 to 20 percent of oil phase, from 0.2 to 5 percent, (weight/vol), preferably, from 0.6 to 2 percent, more preferably, from 0.5 to 1.5 percent of emulsifier and an additive in an amount suitable to control osmolarity, preferably in a range from 1.5 to 5 percent (weight/vol), preferably from 2 to 3 percent.

6. A formulation according to any of claims 1 to 5 wherein the oil phase contains long chain fatty acids in the form of triglycerides in the following proportions by weight:

linoleic acid	40-70%
oleic acid	15-30%
palmitic acid	5-15%
linoleic acid	3-12%
stearic acid	2-6%

7. A formulation according to any claims 1 to 6 wherein the fat emulsion product employed for the preparation of said formulation comprises a composition selected from those reported in the following tables:

	Fat emulsion product 1	Fat emulsion product 2	Fat emulsion product 3
Soybean oil (w/vol)	10%	20%	5%
Safflower oil (w/vol)	--	--	5%
Egg yolk phospholipids (w/vol)	1.2%	1.2%	1.2%
Glycerol (w/vol)	2.25%	2.25%	2.5%
Fatty acids composition of vegetable oils (w/vol)			
Linoleic acid	50%	50%	65.8%
Oleic acid	26%	26%	17.7%
Palmitic acid	10%	10%	8.8%
Linolenic acid	9%	9%	4.2%
Stearic acid	3.5%	3.5%	3.4%
Osmolarity (mOsm/L)	260	268	276
Approximate pH	8	8	8
Fat particle size (μm)	0.5	0.5	0.4
Caloric value (cal/ml)	1.1	2.0	1.1
Size (ml)	50, 100	50, 100	25, 50
	250 or	250 or	100,200
	500	500	Or 500
	Fat emulsion product 4	**Fat emulsion product 5**	**Fat emulsion product 6**
Soybean oil (w/vol)	10%	10%	20%
Safflower oil (w/vol)	10%	--	--
Egg yolk phospholipids (w/vol)	1.2%	1.2%	1.2%
Glycerol (w/vol)	2.5%	2.5%	2.5%

Fatty acids composition of vegetable oil (w/vol)			
Linoleic acid	65.8%	54.5%	54.5%
Oleic acid	17.7%	22.4%	22.4%
Palmitic acid	8.8%	10.5%	10.5%
Linolenic acid	4.2%	8.3%	8.3%
Stearic acid	3.4%	4.2%	4.2%
Osmolarity (mOsm/L)	258	284	292
Approximate pH	8.3	8.3	8.3
Fat particle size (μm)	0.4	0.4	0.4
Caloric value (cal/ml)	2.0	1.1	2.0
Size (ml)	25, 50	100,200	200 or
	200 or	Or 500	550
	500		

and water for injection q.s. to 100%.

8. A formulation according of claims 6 or 7 wherein soybean oil and/or cottonseed oil and/or safflower oil are totally or partially replaced by a mixture of long chain fatty acids in the form of triglycerides to form a composition wherein said fatty acids are present in the respective proportions indicated in said claims and, optionally part of the above oils or long chain fatty acids is substituted by medium chain (C_6-C_{12}) triglycerides.

9. A formulation according to any of claims 1 to 8 wherein the concentration of the oil phase is between 4 and 25% (weight/vol), preferably, between 8 and 18%, more perferably between 8 and 10% of the final formulation.

10. A formulation according to claim 9 wherein the concentration of the oil phase is between 8 and 10% (w/vol) of the final formulation.

11. A formulation according to any one of claims 1 to 10 wherein ramoplanin is present at a concentration between 1 and 20 mg/ml, preferably from 1.5 to 15 mg/ml,most preferably, from about 3 to about 5 mg/ml.

12. A formulation according to any of claims 1 to 11 wherein the pH of the final formulation is lower than 8, preferably, lower than 7.

13. A formulation according to any of claims 1 to 10 wherein the pH of the final formulation is between 4 and 6.5.

14. A formulation according to any one of claims 1 to 13 for treatment of infections caused by agents that are susceptible to ramoplanin or an antibiotic of the ramoplanin family.

15. A formulation according to any one of claims 1 to 13 for the treatment of serious Gram positive infections such as bacteremia, endocarditis or pneumonia.

16. A formulation according to any one of claims 1 to 13 for the treatment of severe infections caused by Gram positive drug-resistant or multiresistant microorganisms such as coagulase positive and negative staphylococci, penicillin-resistant streptococci or glycopeptide resistant enterococci.

17. A formulation according to any one of claims 1 to 16 wherein ramoplanin factor A_2 is present in an amount of at least 75%.

18. A pharmaceutical composition which consists of a ready to use dosage form or of a kit comprising separate packagings or containers containing ramoplanin or a member of ramoplanin family and the fat emulsion product for constitution of a formulation according to any of claims 1 to 17.

19. A kit according to claim 18 which consists of vials or similar containers containing the dose of lyophilised sterile antibiotic, ampuls containing water for injection in amount sufficient to dissolve the antibiotic and bottles containing sterile fat emulsion product in amount appropriate for constituting the desired i.v. formulation.

Declaration and Power of Attorney for Patent Application
Dichiarazione e procura ai fini della domanda di brevetto
Italian Language Declaration

Il sottoscritto inventore dichiara che:

La propria residenza, recapito postale e cittadinanza corrispondono a quanto indicato in calce, sotto la propria firma.

Ritiene di essere il primo ed unico inventore originale (se viene elencato in calce un solo nominativo) o il coinventore primo ed originale (se è elencato più di un nominativo) del oggetto rivendicato e per il quale il sottoscritto presenta domanda di brevetto. La invenzione in questione è chiamata.

_____

_____

_____

e la sua descrizione è allegata alla presente Dichiarazione a meno:

☐ è qui allegato

☐ Il _____

è stata depositata una domanda di brevetto statunitense numero o una domanda di brevetto internazionale PCT numero

_____ che è stata modificata il

_____ (se applicabile)

Il sottoscritto dichiara in oltre di aver letto e compreso il contenuto della descrizione identificata in precedenza, rivendicazioni comprese, come modificati dall'eventuale modifica summenzionata.

Il sottoscritto riconosce l' obbligo di rivelare informazioni essenziali ai fini della determinazione della brevettabilità ai sensi del Titolo 37, Codice dei Regolamenti Federali, § 1.56.

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

NEW INJECTABLE FORMULATIONS
CONTAINING RAMOPLANIN

the specification of which:

☐ is attached hereto.

☐ was filed on _____

as United States Application Number or PCT International Application Number

_____ and was amended on

_____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

Italian Language Declaration

Il sottoscritto rivendica con la presente la priorità prevista dal Titolo 35, Codice degli Stati Uniti, § 119(e)-(d) o § 365(b) in relazione a qualsiasi domanda o domande estere di brevetto o certificato di inventore, o dal Titolo 35, § 365(a) degli stessi Codice in relazione a qualsiasi domanda internazionale PCT nella quale è designato almeno un paese diverso dagli Stati Uniti, i suddetti domande e certifcati essendo elencati sotto, e, spuntando les seguenti caselle, ha anche identificato sotto qualsiasi domanda estera di brevetto o certificato di inventore, o domanda internazionale PCT, la cui data di deposito preceda quella dalla domanda per la quale è rivendicata la priorità.

I hereby claim foreign priority under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below, and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s) (Domande Estere Anteriori)			Priority claimed Diritto di priorità rivendicato	
98114368.8 (Number) (Numero)	EP (Country) (Nazione)	30.07.1998 (Day/Month/Year Filed) (Giorno/Mese/Anno di deposito)	☒ Yes Si	☐ No No
(Number) (Numero)	(Country) (Nazione)	(Day/Month/Year Filed) (Giorno/Mese/Anno di deposito)	☐ Yes Si	☐ No No

Il sottoscritto rivendica con la presente i benefici previsti dal Titolo 35, Codici degli Stati Uniti, § 119(e), in relazione a qualsiasi domanda o domande provvisorie degli Stati Uniti elencate sotto.

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application No.) (N° della domanda)	(Filing Date) (Data di deposito)	(Application No.) (N° della domanda)	(Filing Date) (Data di deposito)

Il sottoscritto rivendica con la presente i benefici previsti dal Titolo 35, Codice degli Stati Uniti, § 120, in relazione a qualsiasi domanda o domande statunitensi, o dal Titolo 35, § 365(c) degli stessi Codice in relazione a qualsiasi domanda internazionale PCT nella quale sono designati gli Stati Uniti, i suddette domande essendo elencate sotto e, nella misura in cui l'oggetto di ciascuna rivendicazione di questa domanda non sia stato esposto nella domanda statunitense o internazionale PCT anteriore nel modo previsto dal primo paragrafo del Titolo 35, Codice degli Stati Uniti, § 112, riconosce l'obbligo di rivelare informazioni essenziali ai fini della determinazione della brevettabilità ai sensi del Titolo 37, Codici dei Regolamenti Federali, § 1.56, le quali diventino disponibili durante il periodo compreso tra la data di deposito della domanda anteriore e la data di deposito nazionale o internazionale PCT della presente domanda.

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(Application No.) (N° della domanda)	(Filing Date) (Data di deposito)	(Status) (patented, pending, abandoned) (Stato) (concessione di brevetto, in corso di esame, abbandono)
PCT/EP99/05137	19 July 1999	pending
(Application No.) (N° della domanda)	(Filing Date) (Data di deposito)	(Status) (patented, pending, abandoned) (Stato) (concessione di brevetto, in corso di esame, abbandono)

Con la presente, il sottoscritto dichiara veritiere tutte le affermazioni contenute in questa domanda in relazione alle proprie conoscenze e di ritenere vere tutte le affermazioni o informazioni presentate. Dichiara inoltre che tali asserzioni sono state espresse nella piena consapevolezza che le dichiarazioni intenzionalmente false sono punibili con una poulte, l' incarcerazione o entrambe, ai sensi della Sezione 1001 del Titolo 18 del Codice degli Stati Uniti e che tali dichiarazioni entenzionalmente false possono mettere a repentaglio la validità della domanda o di qualsiasi brevetto ruasciato in merito.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Italian Language Declaration

PROCURA: Il sootscritto inventore nomina con la presente il seguente avvocato o avvocati e/o agente o agenti al fine di istruire questa pratica e di condurre tutte le operazione ad essa pertinenti presso l'Ufficio dei Brevetti e Marchi di Fabbrica: (Elencare il nome ed il numero di matricola).

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: *(list name and registration number)*

Norman F. Oblon, Reg. No. 24,618; Marvin J. Spivak, Reg. No. 24,913; C. Irvin McClelland, Reg. No. 21,124; Gregory J. Maier, Reg. No. 25,599; Arthur I. Neustadt, Reg. No. 24,854; Richard D. Kelly, Reg. No. 27,757; James D. Hamilton, Reg. No. 28,421; Eckhard H. Kuesters, Reg. No. 28,870; Robert T. Pous, Reg. No. 29,099; Charles L. Gholz, Reg. No. 26,395; William E. Beaumont, Reg. No. 30,996; Jean-Paul Lavalleye, Reg. No. 31,451; Stephen G. Baxter, Reg. No. 32,884; Richard L. Treanor, Reg. No. 36,379; Steven P. Weihrouch, Reg. No. 32,829; John T. Goolkasian, Reg. No. 26,142; Richard L. Chinn, Reg. No. 34,305; Steven E. Lipman, Reg. No. 30,011; Carl E. Schlier, Reg. No. 34,426; James J. Kulbaski, Reg. No. 34,648; Richard A. Neifeld, Reg. No. 35,299; J. Derek Mason, Reg. No. 35,270; Surinder Sachar, Reg. No. 34,423; Christina M. Gadiano, Reg. No. 37,628; Jeffrey B. McIntyre, Reg. No. 36,867; William T. Enos, Reg. No. 33,128; Michael E. McCabe, Jr., Reg. No. 37,182; Bradley D. Lytle, Reg. No. 40,073; and Michael R. Casey, Reg. No. 40,294, with full powers of substitution and revocation.

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(Fornire le stesse informazioni e le firme del terzo e degli ulteriori coinventori.)

(Supply similar information and signature for third and subsequent joint inventors

Italian Language Declaration

Nome per intero di un eventuale terzo co-inventore	Full name of third joint inventor, if any Romeo CIABATTI
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Firma Quinto Inventore Data	Fifth inventor's signature Date
Residenza	Residence
Cittadinanza	Citizenship
Recapito postale	Post Office Address
Nome per intero di un eventuale sesto co-inventore	Full name of sixth joint inventor, if any
Firma del Sesto Inventore Data	Sixth inventor's signature Date
Residenza	Residence
Cittadinanza	Citizenship
Recapito postale	Post Office Address

(Si prega di fornire simili informazioni e firme per il terzo e gli eventuali ulteriori co-inventori.)

(Supply similar information and signature for third and subsequent joint inventors.)